REMARKS

Claims 1, 3-4, 25-27 are currently amended.

Claims 2 and 5 are cancelled.

Claims 6-25 were previously presented.

Claims 1, 3, 4, 6, 19-20, 26-27 are currently pending.

Information Disclosure Statement

Full copies of the publications cited in the Information Disclosure Statement are enclosed. Reconsideration is respectfully requested. A fresh Form PTO-1449 is also enclosed for the Examiner's convenience.

Priority

A certified copy of the French Patent Application will follow in due course.

Claim objections

Claims 1 and 2 are objected to because of the following informalities: Claim 2 recites non-elected subject matter "(i) in Claim 1 and SEQ ID NO.28 in Claim 2."

Claims 1 and 2 have been amended accordingly. Withdrawal of the objection is respectfully requested.

Rejection under 35 USC §112

Claims 3-6, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is now moot for the reasons set forth below.

The definition of the wording "or derivatives thereof" can be found in paragraph [0017] of the application as filed: "*the term derivative is understood to mean a sequence capable of hybridizing under strict conditions with one of the sequence SEQ ID NO. 2, 3 or 4, or with a fragment of these of at least 12 contiguous nucleotides*". This definition is introduced *mutatis mutandis* in the set of claims in replacement of the term "derivative".

It is thus respectfully requested that the rejection under 35 U.S.C. §112(2) be withdrawn.

Rejection under 35 USC §102

Claims 1 and 3 are rejected under 35 USC 102(b) as being anticipated by Surmacz Clinical Cancer Research Vol. 1 (Surmacz).

Surmacz discloses an antisense IRS-1 oligonucleotide having the following nucleotide sequence:

5'-CGC TCG GGA GGC CTA TGG CT-3'

This sequence was designed to hybridize with the 20 bases following the AUG codon of the mouse IRS-1 mRNA.

As helpfully noted by the Examiner, Claims 1 and 3 relate to a composition comprising an antisense oligonucleotide that comprises at least 12 nucleotides that bind to SEQ ID NO:28 (human IRS-1). Hence, a sequence according to Claims 1 and 3 which may hybridize with the 20 bases following the AUG codon of SEQ ID NO:28 has the following sequence:

5'-CGC TCG GGA GGC CTC TCG CT-3'

The antisense IRS-1 oligonucleotide disclosed in Surmacz is thus different from the antisens oligonucleotides disclosed by pending Claims 1 and 3.

Pending Claims 1 and 3 are thus new over Surmacz et al. Withdrawal of the rejection is respectfully requested.

Claim 19 is rejected under 35 USC 102(b) as being anticipated by Wolf et al.

The Examiner indicates that Wolf et al. disclose the human IRS-1 cDNA in vector. The Applicant respectfully submits that the Wolf reference does not seem to be relevant to Claim 19. Wolf et al actually mentions that "*fragments of the human IRS-1 and human SHc cDNAs were subcloned into a pGEX-4T vector using polymerase chain reaction*", without disclosing any of

the specific antisense IRS-1 nucleotide sequences of Claim 19. Thus, Wolf does not disclose every claimed feature.

Pending Claim 19 is thus new over Wolf et al. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC §103

Claims 1, 3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surmacz et al., Nolan et al., and Bennet et al.

According to MPEP 706.02(j), "*35 USC 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references*". However, this rejection is not based on a single reference in view of other references, but on a combination of three publications. It is thus respectfully requested that the rejection be withdrawn.

In any event, Surmacz et al. disclose that the use of a specific mouse antisense sequence of IRS-1 inhibits the proliferation of mouse MCF-7 cells and their oestrogen requirements for growth. First, this sequence is, as previously mentioned, a mouse antisense sequence and is different from those of Claims 1, 3, 5 and 6, which are human antisense sequences. Modifying a nucleotide sequence is not a routine experiment, and it was thus non obvious to design the claimed human antisense sequences from the mouse antisense sequences of the prior art. Second, the sequence described in Surmacz allows the inhibition *in vitro* of the proliferation of plated breast cells MCF-7. There is no obvious connection between the inhibition of the proliferation of breast cells *in vitro* and the inhibition of angiogenesis, which involves endothelial cells and therefore different mechanisms. It was thus non obvious, for one skilled in the art having knowledge of Surmacz et al., to know that the claimed sequences have a strong utility to inhibit angiogenesis in human.

Nolan et al. disclose that the use in MCF-7 cells of a specific antisense sequence of the entire sequence of mouse IRS-1 cDNA resulted in the suppression of anchorage-dependent and -independent MCF-7 cells growth and induced apoptotic cell death under growth factor- and oestrogen-reduced conditions. First, the claimed antisense sequences are not disclosed in Nolan et al. Second, the utility of these antisense sequences to inhibit human angiogenesis is neither taught nor suggested in Nolan et al. It was thus non obvious, for one skilled in the art having knowledge of Nolan et al., to design the claimed anti-angiogenic antisense sequences having a strong utility to inhibit angiogenesis in human.

Bennet et al. disclose compositions and methods for modulating the expression of microtubule-associated protein 4. Bennet et al. teaches away from the claimed subject matter, and it was therefore non obvious for one skilled in the art having knowledge of Bennet et al., to design the claimed anti-angiogenic antisense sequences.

Surmacz et al. and Nolan et al. have used two specific antisense sequences of IRS-1 which are different from the claimed sequences, and from the teaching of Surmacz et al., Nolan et al. or Bennet et al. Thus, it was not obvious to design IRS-1 antisense sequences active on angiogenesis, as claimed by the Applicant.

As a result, Claims 1, 3, 5 and 6 are therefore non obvious over Surmacz et al., Nolan et al., and Bennet et al. Withdrawal of the rejection is respectfully requested.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surmacz et al., Nolan et al., Bennet et al., and further in view of Wolf et al.

As previously mentioned, and according to MPEP 706.02(j), "*35 USC 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references*". However, the instant 35 USC 103 rejection is not based on a

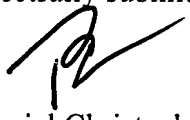
single reference in view of other references but on the simple combination of four publications. It is thus respectfully requested that this 35 USC 103 rejection be withdrawn.

Surmacz et al., Nolan et al. and Bennet et al., and Wolf et al. are as described above. First, none of these references disclose the specific claimed antisense sequences of IRS-1. Second, neither Surmacz et al., Nolan et al., Bennet et al. nor Wolf et al. disclose that the specific antisense sequences of Claim 19 have a strong anti-angiogenic utility. The antisense sequences according to Claim 19 are thus non obvious in view of the cited references.

Accordingly, Claim 19 and its dependent Claim 20 are indeed non obvious over Surmacz et al., Nolan et al., Bennet et al., and Wolf et al. Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, the Applicant respectfully submits that the claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited. Should the Examiner believe that a discussion with the undersigned counsel would expedite prosecution of the application, a telephone call to the undersigned would be welcomed.

Respectfully submitted,



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